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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/069,280	07/24/2002	Deepak Shukla	MIT-108	7876

27130 7590 06/16/2004

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EXAMINER	
MAIER, LEIGH C	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 06/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,280	SHUKLA ET AL.	
	Examiner	Art Unit	
	Leigh C. Maier	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,11-16 and 18-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,11-16 and 18-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 3-10 and 17 have been canceled. Claims 1, 2, 11, 23, and 24 have been amended. (Claim 2 is designated "currently amended" but no change is found. See below.) Claims 25-37 are newly added. Claims 1, 2, 11-16, and 18-37 are pending. Any objection or rejection not expressly repeated has been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

Claims 2 and 20 are objected to because of the following informalities:

Claim 2 is designated as "currently amended," but no change from the previous version is found. Claim 20 is not designated as being amended but contains underlining in line 3. Further regarding claim 20, the words "creams" and "salves" are misspelled.

Appropriate correction is required.

Claim Rejections - 35 USC § 112 – 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-16, 18, 19, 25, and 28-34 are rejected under 35 U.S.C. 112, first paragraph. The claims have been amended to be limited to heparin substrates and products. From the

teaching in ROSENBERG, it appears more likely than not that heparins are available as substrates for 3-OST-3. However, given the differences in structure between heparan and heparins, the process is not enabled to provide products having the oligosaccharide sequences set forth in the claims.

Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

(1) The quantity of experimentation necessary (time and expense);
(2) The amount of direction or guidance presented;
(3) The presence or absence of working examples of the invention;
(4) The nature of the invention;
(5) The state of the prior art;
(6) The relative skill of those in the art;
(7) The predictability or unpredictability of the art; and
(8) The breadth of the claims.

The examiner appreciates that there is not necessarily a bright line distinction between "heparin" and "heparan," but in the art "heparin" typically refers to a GAG that has a greater overall degree of sulfation and very little N-acetylation, while "heparan" has less overall sulfation and about 50% N-acetylation. Therefore, in view of the rarity of unsubstituted glucosamines in these polysaccharides and the rarity of acetylated glucosamines in heparin, it does not appear likely that treatment of heparin with 3-OST-3 would provide the oligosaccharide binding site recited in the claims.

The specification has a single example using heparan sulfate as the substrate. Although chemical techniques are known for modifying heparin, the specification gives no guidance regarding how the structurally different heparin might be modified in such a precise manner to provide the oligosaccharide binding site set forth in the claims. Therefore, one of ordinary skill

would require undue experimentation at great expense in order to make and use the products commensurate with the claims.

Claim Rejections - 35 U.S.C. § 112 – 2nd paragraph

Claims 1, 2, 11-16, and 18-24 are again rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, as set forth in the previous Office action. Newly added claims 25-37 are included in this rejection.

Applicant's arguments filed March 25, 2004 have been fully considered but they are not persuasive.

Applicant cites the "Enriched" passage at page 5 of the specification, stating that "the percentage of 3-OST-3 sulfated polysaccharide in a *typical* unenriched preparation is less than 0.1%." (emphasis added) This is interpreted to mean that less than 0.1% of the glucosamine 3-hydroxyls of the untreated polysaccharides are sulfated. Even though the claims have now been limited to heparins, these polysaccharides are structurally very diverse, as discussed in the previous Office action. There is no single "baseline" heparin. The passage also states "[t]he polysaccharide preparation of the invention are enriched for 3-OST-3 sulfated polysaccharides approximately 10-100 fold." This would modify the polysaccharide to one wherein about 1-10% of the glucosamine 3-hydroxyls of the polysaccharides are sulfated. From this one would surmise that perhaps 1% is the required minimum level of sulfation at this position. However, the passage goes on "the percentage of 3-OST-3 sulfated polysaccharide in the enriched preparations

of the invention is about 5-7%. Therefore, it is still not clear if the minimum required sulfation level is 1%, 5%, or something else.

The rejection regarding the limitation "substantially pure" is withdrawn.

Further regarding claims 19 and 29, the claims lack a period at the end, rendering the claims vague and indefinite.

Further regarding claims 29, the claim recites "the tetrasaccharide sequence" but then goes on to recite the trisaccharide UA2S-GlcNS-IdoA2S. The claim is thus rendered vague and indefinite.

Claim Rejections - 35 U.S.C. § 102

Claims 1, 2, 11, 12, 20, 24-27, and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by LUKAS et al (US 4,465,666) with LINDAHL et al (PNAS, 1980) to support inherency.

The claims have been amended to be limited to heparin substrates and products.

LUKAS teaches the topical administration of heparin for the treatment of herpes virus (refering to the older name HVH, rather than HSV). See col 1, lines 10-20.

As discussed above, heparin is known to be more highly sulfated than heparan. Furthermore, heparin is known to be a more effective anticoagulant than heparan. Applicant admits that HS treated with 3-OST-3 does not have anticoagulant activity, while that treated with 3-OST-1 does. Moreover, it is also known that the 3-O-sulfated glucosamine moiety is critical to heparin's anticoagulant activity. (See LINDAHL) Therefore, one of ordinary skill would conclude that the typical unfractionated heparin is enriched in 3-O-sulfated glucosamines relative

to the typical heparan, the use of heparin, *per se*, to treat HSV-1 would anticipate the instant claims.

Since the Office does not have the facilities for preparing the claimed materials and comparing them with prior art inventions, the burden is on Applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980).

Claims 1, 2, 11, 12, 20, 23-27, and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by LARM et al (WO 98/05341) with LINDAHL et al (PNAS, 1980) to support inherency.

LARM teaches the treatment or prevention of infections caused by herpes virus comprising the administration of sulfated polysaccharides such as heparin. See page 2, lines 2-15; example 1; and example 7. The reference further teaches the preparation of compositions in various forms with preferred heparin concentrations. See page 2, lines 19-24 and page 4, lines 1-11. The use of heparin, *per se*, to treat HSV-1 would anticipate the instant claims for reasons discussed above.

Claim Rejections - 35 U.S.C. § 103

Claims 1, 2, 11, 12, 20-22, 24-27, and 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over LUKAS et al (US 4,465,666).

LUKAS teaches as set forth above. The reference further teaches the use of a composition of heparin in a variety of forms, including gels, lotions, creams, etc. comprising skin penetration enhancers, such as ethanol, propylene glycol, etc., with prefered dosages of heparin. See col 4-5.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to administer a pharmaceutical preparation comprising heparin and a skin penetrating enhancer for the treatment of HSV-1 viral infection. One of ordinary skill would be motivated to prepare and use such a composition with a reasonable expectation of success because LUKAS had taught this utility.

Allowable Subject Matter

Upon further review, it is the opinion of the examiner that the teaching of ROSENBERG would lead the artisan to expect similar products in the treatment of heparan with any of the 3-OST isoforms disclosed therein. That 3-OST-3 provides products that demonstrably different in structure and function is unexpected results. A product/method limited to an enabled substrate (heparan sulfate, *per se*) would be allowable. However, the "contacting . . . with a 3-OST-3 enzyme and a sulfate donor" is not sufficient to define the product because it does not adequately describe the conditions necessary to provide the novel product. Suggested limitations for allowability are incorporation into the independent claims of a structural/functional limitation such as (1) the octasaccharide binding site, as recited in claims 19 and 34; or (2) gD binding constant of 2μM (see page 14 of specification).

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Examiner's hours, phone & fax numbers

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leigh Maier whose telephone number is (571) 272-0656. The examiner can normally be reached on Tuesday, Wednesday, and Friday 7:00 to 3:30 (ET).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson (571) 272-0661, may be contacted. The fax number for Group 1600, Art Unit 1623 is (703) 872-9306.

Visit the U.S. PTO's site on the World Wide Web at http://**www.uspto.gov**. This site contains lots of valuable information including the latest PTO fees, downloadable forms, basic search capabilities and much more.

Leigh C. Maier
Patent Examiner
June 8, 2004

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PRIMARY EXAMINER
GROUP 1600